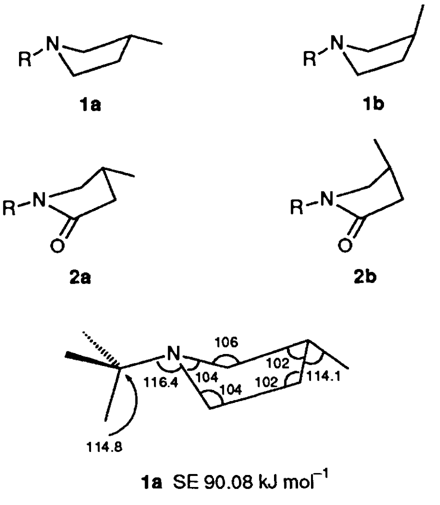
Correlation of Molecular Mechanics with NMR Spectroscopy: Molecular Geometry of Nitrogen Heterocycles

Paul S. Son, Tay-Yean Lin, Thomas Grzybowski, Norman H. Cromwell and Charles A. Kingsbury *
Departments of Chemistry and Mathematics, University of Nebraska-Lincoln, Lincoln, NE 68588-0304, USA

In highly mobile molecules, *e.g.* five-membered rings, the assignment of vicinal coupling constants is difficult due to the similarity of all ^3J values. A way of verifying assignments using MM2 calculations is reported. As MM2 calculations deal with the energy and geometry of individual conformations, whereas NMR data are averaged over all conformations, a way of correlating the two methods of study is provided.

Five-membered rings often do not possess well-defined conformational preferences.[1] The average over a myriad of conformations places most ^3J values near the 'average' value of 7–8 Hz.[2–4] As a result, the assignment of coupling constants to pairs of hydrogens is not straightforward.

Molecular mechanics calculations (*e.g.* MM2) give the energy and geometry of individual conformations.[5] However, the relationship of this geometry to the conformationally averaged NMR parameters is not always evident. The present work provides a way in which NMR data may be correlated with MM2 data. Essentially, this technique involves a summation of weighted coupling constants derived from individual MM2 geometries, which can be compared to ^3J values obtained from the spectrum.[6] The molecules in question are the substituted pyrrolidine **1** (R = Bu^t), and the pyrrolidone **2** (R = Bu^t) (Scheme 1).[7]



Scheme 1

The first step of the correlation procedure is to simulate the NMR spectra using LAOCON in order to obtain coupling constants which are as accurate as possible.[8] Then, MM2 calculations can be performed upon every conceivable conformation of the molecules. The dihedral driver option of MM2 is used to establish an array of energies on either side of the previously-determined energy minima. In some cases, *e.g.* **1** (R = Pr^i), it was also necessary to rotate the exocyclic isopropyl group, as the minimum energy location of this group is not automatically located.

For each conformation (23–99 were used), the predicted NMR coupling constant was calculated. The equation of Altona and co-workers, eqn. (1), was used.[2,9] This equation improves

$$^3J_{HH} = P_1\cos^2\varphi + P_2\cos\varphi + P_3 + \Sigma\Delta X_i[P_4 + P_5\cos^2(\xi_1\cdot\varphi + P_6\cdot|\Delta X_1|)] \quad (1)$$

on the original Karplus relationship[10] by including several types of correction for electronegativity, which is necessary to allow for the effect of nitrogen in these heterocycles. In addition, Altona and co-workers have used a correction for the through-space effects of the tip of the envelope.[11,12]

A somewhat simpler relationship, eqn. (2), has been proposed

$$^3J_{HCCH} = A + B\cos\theta + C\cos 2\theta + \sum_{i=1}^{4}\Delta S_i\cos\theta\cos\varphi_{HX_i} \quad (2)$$

by Gandour and co-workers, which seems to provide similar data.[13] However, eqn. (1) was used in LACA, the calculation program of this study.[14]

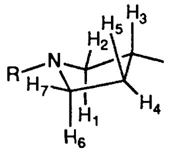
The individual coupling constants are weighted in a Boltzmann relationship using the MM2 steric energies as weighting factors. The resulting coupling constants are summed over all conformations to give an expectation value for the averaged ^3J. Table 1 compares these data to the NMR data from LAOCON simulations. It will be noted that variation exists. This is not entirely due to deficiencies in MM2. In a closely-coupled system, such as **1** or **2** (R = Bu^t), a variety of solutions of the spectrum is possible. The LAOCON simulation was performed by three different persons. Three different results were achieved, differing by as much as ±1 Hz. When the present technique is developed further and accuracy improved, it may be useful as a method to indicate which of several solutions is the more likely.

The greatest discrepancy between predicted and observed coupling constants for **1** (R = Bu^t) occurs for $^3J_{4\text{-}7}$. In several important conformations predicted by MM2, these hydrogens have dihedral angles of *ca.* 90°, and low contributions to the overall ^3J value. In view of the larger observed ^3J, it is possible that MM2 fails to predict the correct average dihedral angle, and/or the correct energies of contributing conformers.[5]

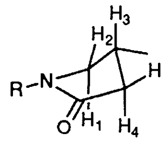
A considerable effort was made to locate other stable contributing conformations. Initial conformations tested involved a number of carbons at the tip of the envelope. Similarly, twist conformations were investigated. These conformations did not show unique energy minima, but many are included as subsets of the rotational profile of the basic conformations (**a** and **b**). Eventually, a Monte Carlo search of geometries was used, which revealed little new information.

The pyrrolidone **2** (R = Bu^t) was predicted by MM2 to have a much more restricted set of conformations. The nitrogen of **2** is part of a rigid and planar amide function. The substituted

Table 1 Predicted *vs.* observed coupling constants



1; R = Bu^t



2; R = Bu^t

Protons	*J*(calc), Hz	Original LCN	LCN3	LCN-5	*J*(calc), Hz	Original LCN	LCN3
1–3	8.3	8.5	7.9	8.4	7.4	7.6	7.5
2–3	6.3	7.9	7.4	8.2	6.7	5.8	6.3
3–4	7.0	7.7	6.6	7.9	7.3	8.4	8.0
3–5	8.8	8.2	8.0	7.6	7.2	6.9	7.2
4–6	8.4	7.7	7.6	7.8			
4–7	4.3	5.1	5.6	5.3			
5–6	5.7	7.8	6.7	7.1			
5–7	8.1	8.2	8.3	8.4			

carbon is at the tip of the envelope. The axial methyl conformer **2b** (R = Bu^t) is predicted to be only 0.5 kcal* less stable than its equatorial counterpart **2a** (R = Bu^t), somewhat similar to **1a** and **1b** (R = Bu^t). However, **2a**, **b** (R = Bu^t) displayed sharp minima, in contrast to the very broad minima for **1a**, **b** (R = Bu^t). Compound **2** (R = Bu^t) has a 'W-shaped' energy minima, with the transition between the two major conformers readily apparent (barrier *ca.* 2 kcal). The rise in energy occurring on rotation past the minimum is quite steep.

trans Hydrogen atoms have a larger coupling constant than *cis* hydrogens in **2**, whereas in **1**, the opposite is usually found. In contrast, the pyrrolidine **1** shows a modest preference for nitrogen to occupy the tip of the envelope. This permits the large N–R group to be staggered with respect to adjacent hydrogens. The nitrogen is considerably flattened, with large bond angles involving the N–R group (Scheme 1). The same occurs to a lesser extent for the 3-Me. However, the energy minima for **1** (R = Bu^t) are broad, *i.e.* a 30° change in dihedral angle on either side of the minimum leads to only +0.3 kcal change in energy. However, the energy *vs.* dihedral angle profile eventually shows sizable increases in energy at large rotations, *i.e.* a 'beaker-shaped' profile exists for **1** (R = Bu^t).

In conclusion, some limitations of the present technique should be pointed out. At the present state of development, it is not possible to take entropy factors into consideration. Thus, if some conformations restrict the side chain and others do not, there is no easy way of incorporating the entropic advantage of the latter. In addition, a difficulty with the use of the dihedral driver option of MM2 is 'lagging'. Allinger has shown that rotation of a given bond does not always result in complementary full rotations elsewhere in the molecule.[15] In contrast to what might have been predicted, lagging is more apparent at low energy changes from the minimum, rather than at higher energies, where a steep energy gradient is present.

In comparison to PSEUROT of de Leeuw *et al.*,[3] the present technique provides a worse fit to the observed coupling constants for **1** (R = Bu^t) (*i.e.* average rms error 1.02, *vs.* rms error 0.28 for the best results achieved using PSEUROT).[16] This technique, however, requires a high level of skill by the user to know whether the results conform to physical reality. On the other hand, LACA is rooted in molecular mechanics, and it reflects the accuracy of this technique, as well as the solution to the spectrum.†

Experimental

The synthesis and properties of the compounds of this study have been reported previously.[7] The NMR data were recorded on a Nicolet WB360 instrument operating at 360.1 MHz. Originally, the LAOCON simulations were performed using the mainframe version of program LAOCN3.[8] This was repeated using LAOCON3 for the IBM PC, and repeated again using LAOCN-5 for 1.[7] The RMS error in the original set was 0.12 on a restricted set of lines, and on the final set using 80% of the major lines, 0.26. The final set was able to accommodate the methyl group, unlike the earlier attempts.

The 1977 version of MM2 was used, modified with 1985 constants. In particular, the following parameters were set for **1**; atoms types 1–8, bond stretch constant *K*(S) = 5.1; distance 1.438 Å; van der Waals' for 8, ε, 0.55, *r*, 1.82; bending parameters for atoms types 1–1–8, *K*(B) = 0.57, θ(0) = 109.47°, for 1–8–1, 0.63, 107.7°; for 5–1–8, 0.5, 108.8°; and for 1–8–20, 0.5, 109.2°; torsional constants, 1–1–8–1, V1 −0.2, V2 0.73, V3 0.8; 1–1–1–8, 0.1, 0.4, 0.5; 5–1–8–1, 0.0, 0.0, 0.52; 5–1–1–8, −0.15, 0.0, 0.15; 5–1–8–20, 0.0, 0.0, 0.0; and 1–1–8–20, 0.2, −0.22, 0.1. For **2**: atom types 3–7, stretching, *K*(S) = 8.0, distance, 1.22; bending, 1–9–3, *K*(B) = 1.93, θ(0) = 117.0°; 1–3–9, 0.66, 114.0°; 7–3–9, 0.67, 124.7°; 1–9–1, 0.76, 126.0°; 1–1–9, 0.42, 110.0°; and 5–1–9, 0.42, 109.0°; torsional, 7–3–9–1, V1 = 0.0, V2 = 5.0, V3 = 0.0; 5–1–3–9, 0.0, 0.0, 0.4; 1–1–9–3, 0.0, 0.0, 0.52; 1–3–9–1, 1.1, 5.0, 0.0; 1–1–9–1, 0.0, 0.0, 0.9; 1–9–1–5, 0.0, 0.0, −0.2; 5–1–9–3, 0.0, 0.0, 0.3; 1–1–3–9, 0.0, 0.0, 0.4; 1–1–1–9; 0.0, 0.0, 0.4; and 5–1–1–9, 0.0, 0.0, 0.4. The general method was to locate all major energy minima by trial and error. The basic conformations involving the *N*-alkyl group axial and equatorial and the 3-Me group axial and equatorial were tested. Then, each ring atom in turn was allowed to occupy the tip of the envelope. Finally, several twist (C_2) conformations were investigated. Then on both sides of the 'best solutions', *i.e.* conformations **a** and **b**, the dihedral driver option was used in 4° increments to establish an energy *vs.* angle of rotation profile. This was also done for some of the minor conformations to test 'hidden minima', if any. For **1** (R = Bu^t), the summation involved 99 conformations (although a smaller number would have sufficed), and for **2** (R = Bu^t), 23 conformations. In practice, conformations higher than *ca.* 1.5 kcal above the minima do not contribute measurably, and these were not considered later in the study. In **1** (R = Bu^t), rotation of other bonds than 2–3–4–5, *e.g.* N–2–3–4, or N–5–4–3, gave

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* 1 cal = 4.184 J.

† The improved parameterization for five-membered rings in MM3 (N. L. Allinger, Y-H. Yuh and J-H. Lii, *J. Am. Chem. Soc.*, 1989, **111**, 8551) may improve the fit to the observed coupling constants.

slightly better data in some instances but much worse in others. The convergence criteria used was that native to MM2, ±0.0001 kcal. The data for **1** (R = Pr^i) is somewhat similar to **1** (R = Bu^t), although the predicted deviations of predicted *vs.* observed *J* are somewhat larger. The Monte Carlo simulations were performed with MMX.[16] Both the 'global optimization of dihedrals' and the 'randomiz' (randomization of *x,y,z* coordinates) options were tested, with several different values of the 'annealing' option tested. The program 'LACA' used to calculate ^3J values includes the Barfield correction (through-space effects).[14]

The calculation involving PSEUROT was found to proceed to a more favourable minimum if at first conformation I was minimized, then conformation II, with the previous results for conformation I held constant, *etc.* Finally, all parameters together were reminimized. When all parameters were minimized from the beginning, the rms errors were seldom better than 1.0. The Barfield correction was not attempted. The initial conformations were similar to **1a** and **1b**, and MM2 parameters were used for the initial geometry $P_1 = 90°$ and $P_2 = 270°$, according to the terminology of Haasnoot, *et al.*, with $\varphi_1 = 43°$ and $\varphi_2 = 43°$. The final minimization gave mole fractions of the two basic conformers similar to the MM2 results for **1a** and **1b** (0.71 and 0.29; MM2: 0.711 and 0.289). However, the geometry of the final conformations were considerably different than **1a** and **1b** ($P_1 = 57.3°$ and $\varphi_1 = 26.5°$; $P_2 = 149.3°$ and $\varphi_2 = 82.9°$). It must be remembered that the PSEUROT data essentially reflect average 'conformations' required to fit the NMR data.

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